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EXAMINER
HUYNH, PHUONG N

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 05/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/046,922	ALITALO ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,12,13 and 21-75* is/are pending in the application.

4a) Of the above claim(s) *39-74* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 12-13, 21-38 and 75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/14/05 has been entered.

2. Claims 1-4, 12-13, and 21-75 are pending.

3. Claims 39-74 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 1-4, 12-13, 21-38 and 75, drawn to an isolated peptide and a composition comprising said peptide, are being acted upon in this Office Action.

5. The disclosure is objected for the following informality: "descubed" at page 14, line 28 should have been "described".

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-4, 12-13, 21-38 and 75 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) an isolated peptide comprising a peptide consisting of the formula: $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID N0: 32) that binds to human VEGFR-3, and wherein the amino acid residue at X_1 is glycine residue, the amino acid residue at X_2 is tyrosine residue, the amino acid residue at X_3 is tryptophan residue, the amino acid residue at X_4 is leucine residue, the amino acid residue at X_5 is threonine residue, the amino acid residue at X_6 is isoleucine residue, and the amino acid residue at X_8 is glycine residue and wherein the polypeptide is 8-100 amino acids in length, (2) the said isolated polypeptide wherein the formula: $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID N0: 32) further comprises amino- and carboxy-terminal cysteine

residues to form a cyclic peptide, (3) the isolated polypeptide comprising a peptide consisting of the amino acid sequence of CGYWLTIWGC (SEQ ID NO: 35) and binds to human VEGFR-3 wherein the polypeptide is 8-100 amino acids in length, (4) An isolated polypeptide comprising a peptide selected from the group consisting of CGYWLTIWGC (SEQ ID NO: 35), SGYWWDTWF (SEQ ID N0: 36), SCYWRDTWF (SEQ ID NO: 37), KVGWSSPDW (SEQ ID N0: 38), FVGWTKVLG (SEQ ID N0: 39), YSSSMRWRH (SEQ ID N0: 40), RWRGNAYPG (SEQ ID NO: 41), SAVFRGRWL (SEQ ID N0: 42), and WFSASLRFR (SEQ ID NO: 43) and wherein the peptide inhibits human Vascular Endothelial Growth Factor c (VEGFR-C) binding to human VEGFR-3 and wherein the polypeptide is 8-100 amino acids in length, (4) A fusion polypeptide comprising a GST or Fc fused to a peptide consisting of the amino acid sequence of CGYWLTIWGC (SEQ ID NO: 35), (5) a labeled polypeptide comprising the isolated polypeptide mentioned above and wherein the label is a radioisotope and (6) a composition comprising the polypeptide mentioned above and a pharmaceutically acceptable carrier for imaging or screening assay, **does not** reasonably provide enablement for any isolated peptide as set forth in claims 1-4, 12-13, 21-38 and 75 for treating any disease such as cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

A. Enablement is not commensurate in scope with the claims as how the make and use any peptide with an amino acid sequence consisting of 8-100 amino acids, wherein the peptide binds to any VEGFR-3 and wherein the amino acid sequence includes $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID NO: 32), wherein the peptide comprises no more than any 3 conserved amino acid substitution at position X1 through X8.

In order to make and use of the claimed invention, one has to be in possession of the peptide sequence and be able to binds human VEGFR-3.

The specification discloses only isolated peptide selected from the group consisting of CGYWLTIWGC (SEQ ID NO: 35), SGYWWDTWF (SEQ ID N0: 36), SCYWRDTWF (SEQ ID NO: 37), KVGWSSPDW (SEQ ID N0: 38), FVGWTKVLG (SEQ ID N0: 39), YSSSMRWRH (SEQ ID N0: 40), RWRGNAYPG (SEQ ID NO: 41), SAVFRGRWL (SEQ ID N0: 42), WFSASLRFR (SEQ ID NO: 43), wherein the peptide binds to human VEGFR-3 (pages 16, and 27). The said peptide further comprises amino and carboxy terminal cysteine residues to form a cyclic peptide. The specification further discloses a peptide dimer comprising a first and second peptide wherein the first and second peptides are the same comprising SEQ ID NO: 35. A composition comprising said peptide or dimer and a pharmaceutically acceptable carrier for imaging or screening assays. There is a lack of guidance as to the structure of peptide with an amino acid sequence consisting of 8-100 amino acids wherein the amino acid sequence "includes" eight amino acids satisfying the formula $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID NO: 32) wherein X1 through X8 are any amino acid substitution without the amino acid sequence. The term "includes" or "including" as defined by the specification to mean "comprising", which is open-ended. There is insufficient guidance as to which amino acids to be added. There is no disclosure of the claimed peptide longer than 8-100 amino acids in length that binds to any VEGFR-3. Further, there is insufficient guidance as to which three amino acids to be substitute for which amino acids for X1 through X8 and whether the peptide still binds to human VEGFR-3. It is not predictable that any peptide with an amino acid sequence consisting of 8-100 amino acids, wherein the amino acid sequence includes any 3 amino acids substitutions at any one of $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID NO: 32), will bind to human VEGFR-3, much less about the binding specificity of the peptide to other VEGFR-3. There are no working examples of such peptide binds to other VEGFR-3. The state of the art with respect to the specificity of receptor binding by VEGF-D is different in mouse and man. For example, it is known that human VEGF-D binds to VEGFR-2 and VEGFR-3. Unlike human VEGF-D that binds to both VEGFR-2 and VEGFR-3, mouse VEGF-D is specific for VEGFR-3 in the mouse, mouse VEGF-D does not bind mouse VEGFR-2 (see Baldwin et al, J Biol Chem 276(22): 19166-19171, 2001; PTO 892). The specification provides no guidance on this point. Further, the specification discloses the cysteine residues are added at the N and Carboxy-terminal end of the formula, not at the N and C-terminal ends of the isolated peptide with an amino acid sequence consisting of 8-100 amino acids. Any peptide with an amino acid sequence consisting of 8-100 amino acids in length having any 3 amino acid substations in $X_1X_2X_3X_4X_5X_6X_7X_8$ that has no resemblance to CGYWLTIWGC is

clearly not enabled. Accordingly, an undue amount of experimentation would be required to determine how to make and use the claimed invention.

B. Enablement is not commensurate in scope with the claims as how the make and use any peptide with an amino acid sequence consisting of 8-100 amino acids, wherein the peptide binds to any VEGFR-3 and comprising the sequence Y_1GYWLTIWGY_2 (SEQ ID NO: 34), wherein Y_1 and Y_2 are any amino acids.

In order to make and use of the claimed invention, one has to be in possession of the peptide and be able to binds human VEGFR-3.

In addition to the problem of the structure of peptide with an amino acid sequence consisting of 8-100 amino acids without the amino acid sequence, and binds to any VEGFR-3, there is insufficient guidance as to the amino acids to be substitute at position Y_1 and Y_2.. Other than cysteines residues at position Y_1 and Y_2, the specification does not teach which amino acids to be substituted and still maintains its cyclic structure and binding to human VEGFR-3. Further, the term "comprising" is open-ended. It expands the peptide to include additional amino acids at either or both ends. There is a lack of guidance as to such amino acids to be added to Y_1GYWLTIWGY_2. There are no working examples of such peptide that binds any other VEGFR-3 other than human VEGFR-3. The specification does not teach any assays that are useful for screening variants and is predictive of success in vivo for treating any disease such as ischemia, lymphedema, restenosis and cancer. The state of the art is that even a single amino acid change in a protein can lead to unpredictable changes in the biological activity of the protein.

Mason *et al* (Molecular Endocrinology 8(3): 325-332, 1994; PTO 892) teach in activin A, even a single amino acid substitution from cysteine to alanine fails to maintain either the structure and/or functions such as intracellular assembly and secretion of the dimer protein (see page 327, column 1, in particular), loss biological activity (See activin cysteine mutant 4 and 12, page 327, column 2, in particular) and loss of receptor binding activity (See Receptor Binding Activities of activin cysteine mutant 4 and 12, page 327, column 2, in particular). Mason *et al* further teach an equivalent protein such as TGFβ1 in which replacing cysteine residue for a serine residue resulted in loss bioactivity (See page 330, column 1, first paragraph, in particular). Given the interaction between the undisclosed peptide and the VEGFR-3 has not been characterized, it would require undue experimentation to determine how to make, and which of the possible polypeptides would be useful for treating which disease.

C. Enablement is not commensurate in scope with the claims as how the make and use any peptide with an amino acid sequence consisting of 7-100 amino acids, wherein the amino acid sequence includes amino acids satisfying the formula $GYWX_1X_2X_3W$ (SEQ ID NO: 67) or $GYWX_1X_2X_3WX_4$ wherein X_1, X_2, X_3 and/or X_4 is any amino acids and wherein the peptide binds any VEGFR-3.

In order to make and use of the claimed invention, one has to be in possession of the peptide sequence and be able to binds human VEGFR-3.

In addition to the lack of guidance as to the rest of the 92 or 93 amino acids in the claimed peptide with an amino acid sequence consisting of 7-100 amino acids, there is insufficient guidance as to which amino acids to be substitute at position X_1, X_2, X_3 and/or X_4. Further, the term "includes" as defined in the specification is meant to be open-ended. It expands the undisclosed amino acids to include additional amino acids at either or both ends. There is a lack of guidance as to such amino acids to be added to either or both ends of $GYWX_1X_2X_3W$ (SEQ ID NO: 67) or $GYWX_1X_2X_3WX_4$. There are no working examples of such peptide that binds to any VEGFR-3 other than human VEGFR-3. There are no in vivo working examples of such peptide could treat any disease. Further, the specification discloses cysteine residues are added at the N and Carboxy-terminal end of the formula, not at the N and C-terminal ends of the isolated peptide with an amino acid sequence consisting of 7-100 amino acids or 8-100 amino acids as now claimed.

with respect to claim 30, in addition to the issues in claims 1 and 21 discussed above, the fusion partner is not recite in the claim 30.

with respect to claims 31, although the fusion partner tumor necrosis factor is recited claim 31, claim 31 depends from claims 1 or 21. Claims 1 and 21 are not enabled for the reasons stated above.

With respect to claims 32, although the fusion partner antibody or fragment thereof is recited claim 32, claim 32 depends from claims 1 or 21. Claims 1 and 21 are not enabled for the reasons stated above. Further, there is insufficient guidance as to the binding specificity of the antibody and which "fragment" of the antibody is part of the chimeric protein.

With respect to claim 33, the only modification to increase the circulating in-vivo half-life of the peptide as disclosed in the specification is to fuse the peptide to the Fc fragment of an antibody, not just any fragment of an antibody. The term "modification" encompasses any modification of an isolated peptide of claims 1 or 21. The specification does not teach modifying

which amino acids within the peptide that has 8-100 amino acids in length is to be substituted, deleted, added or combination thereof such that the modified peptide increases in vivo half-life. With respect to the argument that glycosylation, pegylation are disclosed in the specification. The claim does not recite the specific modification such as the peptide is glycosylated or pegylated.

With respect to claim 34, claim 34 recites a peptide dimer comprising first and second peptide monomers, wherein at least one of the peptide moners comprises "a" peptide according to any one of claims 1 or 21 and wherein the dimer binds to VEGFR-3. The claims encompass any peptide dimer wherein one of the peptide monomer is from any fragment of a peptide from claims 1 or claim 21 and wherein the dimer binds to any VEGFR-3. Claims 1 and 21 are not enabled for the reasons stated above. Assuming one of the monomer in the dimer is from the peptide recited in claims 1 or 21, there is insufficient guidance as to the structure of the other monomer in the claimed peptide dimer. Further, the term "a peptide" instead of the peptide according claims 1 or 21 mean any fragment the peptide according to claims 1 or 21. There is a lack of guidance as to which fragment such as one or two amino acids of the peptide according to claims 1 or 21 is useful for forming dimer and still binds to human VEGFR-3. There are no working examples of such dimer binds to any VEGFR-3 other than human VEGFR-3.

With respect to claims 35-36, claims 1 and 21 are not enabled for the reasons stated above. The term "comprising" is open-ended. There is insufficient guidance as to the structure of the first and second peptide monomers without the amino acid sequence, much less the function of such peptide dimer.

With respect to claim 37, claims 1 and 21 are not enabled for the reasons stated above. Further, none of the peptides in the specification as filed has been shown to bind to any VEGFR-1, any VEGFR-2, any neuropilin-1 (NP-1) and any neutopilin-2 (NP-2) other than human VEGFR-3. See Brenner v. Manson, 383 U.S. 519, 535-36, 148 USPQ 689, 696 (1966), noting that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." Until the structure of the peptides that bind to any and all VEGFR-1, VEGFR-2, neuropilin-1 (NP-1) and neutopilin-2 (NP-2) have been identified, the specification merely extends an invitation to one skill to come up with the structure of the claimed peptide.

With respect to claim 38, since the structure of peptide in claims 1 and claim 21 are not enabled, it follows that any composition comprising such peptide and a pharmaceutical acceptable carrier is not enabled.

Given the structures of any of the peptide mentioned above are not enabled, it follows that any dimer, chimeric protein, any peptide attached to any antibody or antibody fragment, prodrug, radioisotope, cytotoxic agent, and composition comprising any peptide mentioned above are not enabled.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 11/14/05 have been fully considered but are not found persuasive.

Applicants' position is that the claims are directed to peptides of 8-100 amino acids, wherein the peptide includes a particular sequence of amino acids recited in the claims. Applicants have fully enabled a worker of ordinary skill in the art to make and use a peptide of 8-100 amino acids comprising the claimed shorter peptides. For example, the specification at page 35, line 8, to page 38, line 6, teaches methods for making peptides of varying lengths using techniques common in the art such as solid phase synthesis, preparation from a phage library, and recombinant expression systems. The specification indicates that a worker of ordinary skill can prepare a phage display library having peptides of a desired length range, e.g., from 4 to about 80 amino acids (Koivunen et al., J. Nucl. Med. 40:883-88, 1999; Heiskanen et al., Virology 262:321-32, 1999, abstracts inclùded), and also teaches that the peptide may be a part of a fusion protein or a chimeric protein, e.g. a GST fusion protein (see page 38). The specification provides guidance as to which peptides of the invention would exhibit binding to VEGFR-3. The specification provides numerous working examples of peptides isolated from a phage display library that bind VEGFR-3 (see Table 1). There is no reason to expect that screening the binding of larger peptides would be more burdensome. With respect to claim 12, the claim at issue explicitly states that positions Y1 and Y2 are contemplated to be amino acids. The specification

discloses the residues may be any amino acids at page 16 , lines 3-7 and page 17, lines 11-16 and sets out exemplary peptides of the invention wherein the "Y1" or "Y2" residues are cysteines.

In response, the claims are directed to any peptides of 8-100 amino acids, wherein the peptide includes a particular sequence of amino acids having any amino acid substitution at $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID NO: 32) and binds to any VEGFR-3. The claims are not drawn a peptides of 8-100 amino acids, wherein the peptide includes a specific sequence of amino acids selected from the group consisting of CGYWLTIWGC (SEQ ID NO: 35), SGYWWDTWF (SEQ ID N0: 36), SCYWRDTWF (SEQ ID NO: 37), KVGWSSPDW (SEQ ID N0: 38), FVGWTKVLG (SEQ ID N0: 39), YSSSMRWRH (SEQ ID N0: 40), RWRGNAYPG (SEQ ID NO: 41), SAVFRGRWL (SEQ ID N0: 42), and WFSASLRFR (SEQ ID NO: 43) and wherein the peptide inhibits human Vascular Endothelial Growth Factor c (VEGFR-C) binding to human VEGFR-3. In order to make, of the claimed invention, the structure, i.e. amino acid sequence is required. One of skill in the art cannot contemplate the structure of the peptide that is not clearly disclosed. With regard to fusion protein, the fusion partner must also be recite in the claim in addition to the peptide.

In response to applicant's argument that the specification provides guidance as to which peptides of the invention would exhibit binding to VEGFR-3, the claims are not drawn to the specific peptide that binds to human VEGFR-3. There is no disclosure of the claimed peptide longer than 8-100 amino acids in length binds to any VEGFR-3. Other than the specific peptide that binds to human VEGFR-3, there are no working examples of such peptide that binds to other VEGFR-3. The state of the art with respect to the specificity of receptor binding by VEGF-D is different in mouse and man. For example, it is known that human VEGF-D binds to VEGFR-2 and VEGFR-3. Unlike human VEGF-D that binds to both VEGFR-2 and VEGFR-3, mouse VEGF-D is specific for VEGFR-3 in the mouse, mouse VEGF-D does not bind mouse VEGFR-2 (see Baldwin et al, J Biol Chem 276(22): 19166-19171, 2001; PTO 892). The specification provides no guidance on this point. Further, the specification discloses the cysteine residues are added at the N and Corboxy-terminal end of the formula, not at the N and C-terminal ends of the isolated peptide with an amino acid sequence consisting of 8-100 amino acids as now claimed. Accordingly, an undue amount of experimentation would be required to determine how to make and use the claimed invention.

In response to the argument with respect to claim 12, claim 12 encompasses any peptide of 8-100 amino acids, wherein the peptide comprises the sequence Y1 GYWLTIWGY2 wherein the peptide binds to any VEGFR-3 and wherein Y1 and Y2 are any amino acids. There is a lack of guidance as to the structure of peptide with an amino acid sequence consisting of 8-100 amino acids without the amino acid sequence. Although the specification discloses the positions Y1 and Y2 are contemplated to be any one of amino acids disclosed at page 16, lines 3-7 and page 17, lines 11-16 and sets out exemplary peptides of the invention wherein the "Y1" or "Y2" residues are cysteines, none of such amino acids are recited in claim 12. Further, since the length of the peptide is 8-100 amino acids in length, the formula is only eight amino acids residues, the rest of the 92 amino acids within the claim peptide is not adequate disclosed. The specification discloses peptide GYWLTIWGY binds only to human VEGFR-3 (see page 16). The specification does not teach any peptide ranging from shortest (8 amino acids) to the longest (100 amino acids) binds to any VEGFR-3 other than human VEGFR-3. There are no working examples of such peptide binds to other VEGFR-3. The state of the art with respect to the specificity of receptor binding by VEGF-D is different in mouse and man. For example, it is known that human VEGF-D binds to VEGFR-2 and VEGFR-3. Unlike human VEGF-D that binds to both VEGFR-2 and VEGFR-3, mouse VEGF-D is specific for VEGFR-3 in the mouse, mouse VEGF-D does not bind mouse VEGFR-2 (see Baldwin et al, J Biol Chem 276(22): 19166-19171, 2001; PTO 892). The specification provides no guidance on this point. Accordingly, an undue amount of experimentation would be required to determine how to make and use the claimed invention.

In response to the argument with respect to claims 21 and 22, the term includes is open-ended. It expands the amino acids at either or both ends. There is insufficient guidance as to which amino acids to be added at. Further, 3 out of the 7 residues in GYWX1X2X3W or 4 out of the 8 amino acids in the formula GYWX1X2X3W are any amino acids. A peptide with an amino acid sequence consisting of 100 amino acids in length and 94 out of the 100 amino acids of such peptide are undisclosed. It is not routine for one of skill in the art to second-guess the structure of the claimed peptide. There are no working examples of such peptide from shortest to the longest binds to any VEGFR-3 other than human VEGFR-3. It is not routine to treat any disease such as cancer with a peptide that is 100 amino acids in length and 94 out of the 100 amino acids of such peptide are undisclosed. Further, the specification discloses cysteine residues are added at the N and Carboxy-terminal end of the formula, not at the N and C-terminal ends of the isolated peptide

with an amino acid sequence consisting of 7-100 amino acids or 8-100 amino acids as now claimed.

In response to the argument with respect to claim 30, the fusion partner is not recite in the claim in addition to the issues discussed above for claim 1 and 21, which are incorporated here by reference.

In response to the argument with respect to claims 31, although the fusion partner tumor necrosis factor is recited claim 31, claim 31 depends from claims 1 or 21. Claims 1 and 21 are not enabled for the reasons stated above.

In response to the argument with respect to claims 32, although the fusion partner antibody or fragment thereof is recited claim 32, claim 32 depends from claims 1 or 21. Claims 1 and 21 are not enabled for the reasons stated above. Further, there is insufficient guidance as to the binding specificity of the antibody and which fragment of the antibody is part of the chimeric protein.

With respect to claim 33, the only modification to increase the circulating in-vivo half-life of the peptide as disclosed in the specification is to fuse the peptide to the Fc fragment of an antibody, not just any fragment of an antibody. The term "modification" encompasses any modification of an isolated peptide of claims 1 or 21. The specification does not teach modification in which amino acids within the peptide that has 8-100 amino acids in length is to be substituted, deleted, added or combination thereof such that the modified peptide increases in vivo half-life. With respect to the argument that glycosylation, pegylation are disclosed in the specification. The claim does not recite the specific modification such as the peptide is glycosylated or pegylated.

With respect to claim 34, claim 34 recites a peptide dimer comprising first and second peptide monomers, wherein at least one of the peptide moners comprises "a" peptide according to any one of claims 1 or 21 and wherein the dimer binds to VEGFR-3. The claim encompasses any peptide dimer wherein one of the peptide monomer is from any fragment of a peptide from claims 1 or claim 21 and wherein the dimer binds to any VEGFR-3. Claims 1 and 21 are not enabled for the reasons stated above. Assuming one of the monomer in the dimer is from the peptide recited in claims 1 or 21, there is insufficient guidance as to the structure of the other monomer in the claimed peptide dimer. Further, the term "a peptide" instead of the peptide according claims 1 or 21 mean any fragment the peptide according to claims 1 or 21. There is a lack of guidance as to which fragment such as one or two amino acids of the peptide according to claims 1 or 21 is

useful for forming dimer and still binds to human VEGFR-3. There are no working examples of such dimer binds to any VEGFR-3.

With respect to claims 35-36, claims 1 and 21 are not enabled for the reasons stated above. The term "comprising" is open-ended. There is insufficient guidance as to the structure of the first and second peptide monomers without the amino acid sequence, much less the function of such peptide dimer.

With respect to claim 37, claims 1 and 21 are not enabled for the reasons stated above. Further, none of the peptides in the specification as filed has been shown to bind to any VEGFR-1, any VEGFR-2, any neuropilin-1 (NP-1) and any neutopilin-2 (NP-2) other than human VEGFR-3. . See Brenner v. Manson, 383 U.S. 519, 535-36, 148 USPQ 689, 696 (1966), noting that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." Until the structure of the peptide that binds to any and all VEGFR-1, VEGFR-2, neuropilin-1 (NP-1) and neutopilin-2 (NP-2) has been identified, the specification merely extends an invitation to one skill to come up with the structure of the claimed peptide.

With respect to claim 38, since the structure of peptide in claims 1 and claim 21 are not enabled, it follows that any composition comprising such peptide and a pharmaceutical acceptable carrier is not enabled.

8. Claims 1-4, 12-13, 21-38 and 75 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) any isolated peptide with an amino acid sequence consisting of 8-100 amino acids, wherein the peptide binds to VEGFR-3 and wherein the amino acid sequence includes $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID NO: 32), wherein the peptide comprises no more than any 3 conserved amino acid substitution at position X1 through X8, (2) any isolated peptide with an amino acid sequence consisting of 8-100 amino acids, wherein the peptide binds to VEGFR-3 and wherein the amino acid sequence includes $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID NO: 32), wherein the peptide comprises no more than any 3 conserved amino acid substitution at position X1 through X8 further comprising amino- and carboxy-terminal cysteine residues, (3) any isolated peptide with an amino acid sequence consisting of 8-100 amino acids, wherein the peptide binds to VEGFR-3 and wherein the amino

acid sequence includes $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID NO: 32), wherein the peptide comprises no more than any 3 conserved amino acid substitution at position X1 through X8 wherein the amino acid sequence satisfied the formula: C $X_1X_2X_3X_4X_5X_6X_7X_8$C (SEQ ID NO: 33), (4) any isolated peptide with an amino acid sequence consisting of 8-100 amino acids, "comprising" the sequence Y1GYWLTIWGY2 (SEQ ID NO: 34), wherein Y1 and Y2 are any amino acids, (5) any isolated peptide with an amino acid sequence consisting of 8-100 amino acids, wherein said peptide "comprises" the sequence CGYWLTIWGC (SEQ ID NO: 35), (6) any isolated peptide with an amino acid sequence cosseting of 7-100 amino acids wherein the amino acid sequence includes amino acids satisfying the formula GYW $X_1X_2X_3$W (SEQ ID NO: 67), wherein X_1X_2 and X_3 comprises any amino acids and wherein the peptide binds VEGFR-3, (7) any isolated peptide with an amino acid sequence cosseting of 7-100 amino acids wherein the amino acid sequence satisfying the formula GYW $X_1X_2X_3WX_4$ (SEQ ID NO: 68), wherein $X_1X_2X_3$ and X_4 comprises any amino acids and wherein the peptide binds VEGFR-3, (8) any isolated peptide with an amino acid sequence cosseting of 7-100 amino acids wherein the amino acid sequence includes amino acids satisfying the formula GYW $X_1X_2X_3$W (SEQ ID NO: 67), wherein X_1X_2 and X_3 comprises any amino acids and wherein the peptide binds VEGFR-3 further comprising amino- and carboxy-terminal cysteine residues or any isolated peptide with an amino acid sequence cosseting of 7-100 amino acids wherein the amino acid sequence satisfying the formula GYW $X_1X_2X_3WX_4$ (SEQ ID NO: 68), wherein $X_1X_2X_3$ and X_4 comprises any amino acids and wherein the peptide binds VEGFR-3, further comprising amino- and carboxy-terminal cysteine residues, and (9) any isolated peptide as set forth in claims 29 and 32-34, and 36-37 (10) any chimeric protein as set forth in claims 30-31, (11) any peptide dimer as set forth in claim 35 and (12) any composition comprising any isolated peptide mentioned above in a pharmaceutically acceptable carrier.

The specification discloses only an isolated peptide selected from the group consisting of CGYWLTIWGC (SEQ ID NO: 35), SGYWWDTWF (SEQ ID N0: 36), SCYWRDTWF (SEQ ID NO: 37), KVGWSSPDW (SEQ ID N0: 38), FVGWTKVLG (SEQ ID N0: 39), YSSSMRWRH (SEQ ID N0: 40), RWRGNAYPG (SEQ ID NO: 41), SAVFRGRWL (SEQ ID N0: 42), WFSASLRFR (SEQ ID NO: 43), wherein the peptide binds to human VEGFR-3 (page 16). The specification further discloses an isolated polypeptide with an amino acid sequence consisting of 8-100 amino acids comprising the peptide CGYWLTIWGC (SEQ ID NO: 35) wherein the binds to human VEGFR-3. A peptide dimer comprising first and second peptide consisting of the amino acid sequence of CGYWLTIWGC (SEQ ID NO: 35). A fusion or

chimeric protein comprising the peptide consisting of the amino acid sequence of CGYWLTIWGC (SEQ ID NO: 35) fused to the Fc fragment of an immunoglobulin or GST.

With the exception of the specific peptide mentioned above, there is insufficient written description about the structure associated with function of any isolated peptide with an amino acid sequence consisting of 8-100 amino acids, wherein the peptide binds to any VEGFR-3 and wherein the amino acid sequence includes $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID NO: 32), wherein the peptide comprises no more than any 3 conserved amino acid substitution at position X1 through X8. This is because an isolated peptide without the amino acid sequence has no structure, much less binding to any VEGFR-3. For the sake of illustration, assuming a peptide that is 100 amino acids in length and has 3 specified conservative amino acids substitution in the formula, this is equivalent to a peptide with 97 amino acids out of the 100 amino acid residues that are not adequately described. The term "includes" or "including" as defined by the specification to mean "comprising", which is open-ended. There is inadequate written description about the amino acids to be added. There is no disclosure of any peptide longer than 100 amino acids in length that binds to any VEGFR-3. Further, there is inadequate written description about which three amino acids to be substitute for which amino acids within the X1 through X8 and whether the peptide still binds to human VEGFR-3, much less about the binding specificity of the peptide to other VEGFR-3. Further, the specification discloses the cysteine residues are added at the N and Carboxy-terminal end of the formula, not at the N and C-terminal ends of the isolated peptide with an amino acid sequence consisting of 9-100 amino acids. Any peptide with an amino acid sequence consisting of 8-100 amino acids in length having any 3 amino acid substations in $X_1X_2X_3X_4X_5X_6X_7X_8$ that has no resemblance to CGYWLTIWGC is clearly not adequately described. The same reasoning applies to claim 3. With regard to claim 4, although the specific conservative amino acids substitution are recited in the claim, there is inadequate written description about the specific combination of amino acid substitution in $X_1X_2X_3X_4X_5X_6X_7X_8$ in a peptide of 8-100 amino acids in length. Even assuming the $X_1X_2X_3X_4X_5X_6X_7X_8$ are adequate described, the rest of the 92 amino acids are not adequately described without the amino acid sequence. Again, none of the peptides discloses in the specification as filed bind to any VEGFR-3 other than human VEGFR-3.

With regard to claim 12, the specification discloses Y1 and Y2 are cysteine. The specification does not adequate describe any with an amino acid sequence consisting of 8-100 amino acids, wherein the peptide binds to any VEGFR-3 and wherein the amino acid sequence

includes Y1GYWLTIWGY2 (SEQ ID NO: 34) wherein Y1 and Y2 are any amino acids. This is because 92 amino acid residues in such peptide are not adequately described. No such peptide binds to VEGFR-3 from other species is ever disclosed. The term "comprising" is open-ended. It expands the peptide to include additional amino acids at either or both ends. There is a lack of disclosure about the amino acids to be added to $Y_1GYWLTIWGY_2$.

With regard to claim 13, since the peptide is within the amino acid sequence consisting of 8-100 amino acids in length, the rest of the 90 amino acids are not adequately described without the amino acid sequence. Further, the term "comprises" is open-ended. It expands the peptide to include additional amino acids at either or both ends. There is a lack of disclosure about the amino acids to be added to CGYWLTIWGC. The same reasoning applies to claims 21-29.

With respect to claim 30, in addition to the issues in claims 1 and 21 discussed above, the fusion partner is not recite in the claim 30 is not adequate described.

With respect to claims 31, although the fusion partner tumor necrosis factor is recited claim 31, claim 31 depends from claims 1 or 21. Claims 1 and 21 are not adequately described for the reasons stated above.

With respect to claims 32, although the fusion partner antibody or fragment thereof is recited claim 32, claim 32 depends from claims 1 or 21. Claims 1 and 21 are not adequately described for the reasons stated above. Further, there is inadequate disclosure about the binding specificity of the antibody and which fragment of the antibody is part of the claimed chimeric protein.

With respect to claim 33, the only modification to increase the circulating in-vivo half-life of the peptide as disclosed in the specification is to fuse the peptide to the Fc fragment of an antibody, not just any fragment of an antibody. The term "modification" encompasses any modification of an isolated peptide of claims 1 or 21. The specification does not disclose which amino acids within the peptide that has 8-100 amino acids in length is to be substituted, deleted, added and/or combination thereof such that the modified peptide increases in vivo half-life. The specification also discloses glycosylation, and pegylation. However, the claim does not recite the specific modification such as the peptide is glycosylated or pegylated.

With respect to claim 34, claim 34 recites a peptide dimer comprising first and second peptide monomers, wherein at least one of the peptide moners comprises "a" peptide according to any one of claims 1 or 21 and wherein the dimer binds to VEGFR-3. The claim encompasses any peptide dimer wherein one of the peptide monomer is from any fragment of a peptide from claims

1 or claim 21 and wherein the dimer binds to any VEGFR-3. Claims 1 and 21 are not adequately described for the reasons stated above. Assuming one of the monomers in the peptide dimer is from the peptide recited in claims 1 or 21, the structure of the other monomer in the claimed peptide dimer is not adequately described. Further, the term "a peptide" instead of "the peptide" according claims 1 or 21 means any fragment of the peptide according to claims 1 or 21. There is no disclosure about which fragment such as one or two amino acids of the peptide according to claims 1 or 21 is useful for forming dimer and still binds to human VEGFR-3.

With respect to claims 35-36, claims 1 and 21 are not adequately described for the reasons stated above. The term "comprising" is open-ended. It expands the peptide to include additional amino acids at either or both ends. As such, the structures of the first and second peptide monomers without the amino acid sequences that bind to any VEGFR-3 are not adequately described.

With respect to claim 37, claims 1 and 21 are not adequately described for the reasons stated above. Further, none of the peptides in the specification as filed has been shown to bind to any VEGFR-1, any VEGFR-2, any neuropilin-1 (NP-1) and any neutopilin-2 (NP-2) other than human VEGFR-3. As such, any peptide that binds to any VEGFR-1, any VEGFR-2, any neuropilin-1 (NP-1) and any neutopilin-2 (NP-2) without the amino acid sequence is not adequately described.

With respect to claim 38, since the structure of peptide in claims 1 and claim 21 are not adequately described, it follows that any composition comprising such peptide and a pharmaceutical acceptable carrier is not described.

The specification discloses only peptides that are 10 amino acids in length and binds only human VEGFR-3, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of peptide with an amino acid sequence consisting of 8-100 or 7-100 amino acids in length that bind to any VEGFR-3, any VEGFR-1, any VEGFR-2, any neuropilin-1 (NP-1) or any neuropilin (NP-2) to describe the genus for the claimed peptide. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

9. Claims 2 and 23 rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection**.

The "isolated peptide with an amino acid sequence consisting of 8-100 amino acids ...further comprising amino- and carboxy-terminal cysteine residues" in claim 2 represents a departure from the specification and the claims as originally filed. The specification at page 15 discloses the cysteine residues are located at the amino- and carboxy-terminal of formula $CX_1X_2X_3X_4X_5X_6X_7X_8C$ to form a cyclic peptide. The claim as written, the cysteine residues are located at the amino- and carboxy-terminal of a peptide consisting of 9, or 10... to 100 amino acids in length.

The "isolated peptide with an amino acid sequence consisting of 7-100 amino acids ...further comprising amino- and carboxy-terminal cysteine residues" in claim 23, represents a departure from the specification and the claims as originally filed. The specification at page 17 discloses the cysteine residues are located at the amino- and carboxy-terminal of the peptide $GYWX_1X_2X_3WX_4$ to form a cyclic peptide.

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

12. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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